

Effectiveness of Smear Technique in Detection of Pulmonary and Gastric Cancer

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SUMMARY

In the initial use of cytologic examination of smears to detect pulmonary and gastric cancer at the Los Angeles County Hospital during the period April 1949 to June 1950, 350 patients with suspicion of pulmonary disease and 128 with gastric problems were studied. In the pulmonary group, 80 per cent of 51 malignant lesions were diagnosed by the smear technique. Sixty per cent of 15 neoplasms in the stomach were diagnosed by the method.

The results are analyzed in terms of sensitivity, accuracy, reliability and "yield" for the method. Cytological criteria of the presence of malignant disease are given and illustrated by photomicrographs.

The method is one of potentially great value as an aid to diagnosis. Use of it in examination of selected categories of patients seems warranted.

SINCE Papanicolaou and Traut⁹ in 1943 revived interest in the cytological study of smears of body secretions for detection of exfoliated malignant cells, many investigators have demonstrated the usefulness of this method in the early diagnosis of cancer. The following presentation is a report on the initial routine use of the method at the Los Angeles County Hospital during the period April 1949 through June 1950 with regard to diagnosis of pulmonary and gastric cancer.

MATERIALS AND METHODS

Pulmonary Studies

Smear studies were made in 350 cases. The patients were from various services as follows: Tuberculosis, 56.8 per cent; medical, 26 per cent; surgical, 8 per cent; miscellaneous, 9.2 per cent.

The ideal study was considered to consist of at least two daily sputa following bronchoscopy (or else a series of five daily sputa), but many cases were studied much less thoroughly: Bronchial specimen and sputa, 52.2 per cent; single bronchial specimen only, 23.2 per cent; single sputum specimen only, 14.3 per cent; two or more sputum specimens, 10.3 per cent.

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Smears were made directly from aspirated bronchial exudate if there was enough of such material, and if not they were made from material recovered from saline irrigations. Sputa varied in quality but early morning deep cough specimens were requested. During the period of this report, in an effort to build up the cytology service, no specimens were rejected as unsatisfactory. Therefore, many smears which were too thin or which for other reasons would not meet the present standards were included. (At present the general criteria for acceptability outlined by Graham and co-workers¹⁵ are followed. Specimens of sputum that do not contain macrophages are rejected, as are bronchial secretions containing only a few columnar epithelial cells or with only erythrocytes and leukocytes.) In the laboratory, the usual techniques were employed—prompt fixation in alcohol-ether, and staining by the Papanicolaou-Traut method.⁹ From three to five smears from each specimen were screened. Abnormal cells were evaluated by the criteria of malignancy as defined by Farber and co-workers.³

Gastric Studies

In most of the 128 cases in which smears of gastric material were studied, the patients were subjects for gastroscopy. Thirteen per cent of them were patients in the medical service, 12 per cent in the surgical service, 74 per cent in the gastroenterology clinic, and 1 per cent in other services. Ordinarily the specimen consisted of 20 to 40 ml. of thick mucus aspirated from the fasting stomach via Levine tube for routine gastric analysis preliminary to endoscopy. Smears were made from "fished" particulate matter or, when practicable, from centrifuged sediment. It was not generally necessary to use any adhesive.

As a rule, no pertinent clinical data were available at the time the smears were examined. Liebow and co-workers⁶ held, in reference to pulmonary cases, that for a critical analysis of the method, the examiner should know nothing about the patient. Bryant and his co-workers¹ concluded, from a study of gastric aspirates, that this was an added hazard to accurate reporting rather than an aid to scientific honesty. The authors believe that strict adherence to cytological criteria of malignant process, without foreknowledge of clinical data, results in more accurate diagnosis.

REPORTING

If results of examination of smears were positive for cancer, the report given was, "consistent with malignancy." So far as could be determined, there

were no "false positives." Histological evidence of malignant lesion was present in all but two of the 36 proven cases of pulmonary cancer detected by smear (see under *Histology*). If results of smear examination were negative, the report was, "no malignancy." In cases in which "no malignancy" was reported and it was later determined by other means that carcinoma was present, the slides were reviewed. If previously overlooked malignant or suspicious cells then were noted, the original report was considered to have been "false negative." If no such cells were observed in reexamination, the diagnosis was considered "missed." "Inconclusive" was a non-committal diagnosis; but included among the cases in which the smears were reported as "inconclusive" were some in which there were "suspicious" cells, implying that malignant disease was probable and that examination of additional specimens was important. If malignant disease was found to be present in a case in which the report was only "inconclusive,"

the result of the smear examination was tabulated as a "miss"; but if the term "suspicious" was used in the report, the presence of the lesion was deemed to have been "detected" by the smear technique. "Misses" in which there were recorded (but unreported) impressions of atypical and metaplastic cells have since been reviewed in terms of Papanicolaou's classification.⁷

The classifications used in the cytologic service of the Los Angeles County Hospital were matched with Papanicolaou's designations as follows:

Los Angeles County Hospital Classification	Equivalent in Papanicolaou Classification
Negative (unequivocally).....	I
Negative (with atypical cells).....	II
Inconclusive (with atypical cells).....	III
Suspicious (probably positive).....	IV
Positive (unequivocally).....	V

As Papanicolaou's seemed superior to the system in use, it was adopted.

Of the 478 patients studied, 66 had tumors—proven in 49 cases. The 17 cases in which the presence of cancer was still unproven at the time of this report are included for purposes of discussion. Data indicating the sensitivity, reliability and accuracy of the method as it was employed in the period covered by this report are given in Table 1. Table 2 gives data for the separate and combined series (pulmonary and gastric) as to the grouping of the patients examined, sex, and age by decades. The kind of specimens examined is shown in Table 3.

TABLE 1.—Data on Sensitivity, Reliability and Accuracy of Cytologic Diagnosis of Cancer

SENSITIVITY			
	Total	Pulmonary	Gastric
Cases studied.....	478	350	128
Total tumors.....	66	51	15
"Detected" tumors.....	50 (75.8%)	41 (80.4%)	9 (60%)
RELIABILITY			
"Missed" tumors.....	14 (21.2%)	8 (15.6%)	6 (40%)
"False-negative" diagnoses.....	2 (3%)	2 (3.9%)	0
"False-positive" diagnoses.....	0	0	0
ACCURACY			
Cytologic Report	Papanicolaou Equivalent	Detected	
"Consistent with malignancy".....	V}	38	8
"Inconclusive".....	IV}	3	1
		Missed	
"Inconclusive".....	III}	1	0
"No malignancy".....	II}	3	2
"No malignancy".....	I}	4	4

TABLE 3.—Materials Examined in Attempt to Detect Pulmonary Tumors

Material	% of patients giving Specimen	% of patients with Tumors	% of Tumors
Bronchial and sputa....	52	12	43
One bronchial specimen only.....	23	21	33
One sputum only.....	15	12	12
Two or more sputa....	10	16	12

TABLE 2.—Data on Detection of Pulmonary and Gastric Cancer by Examination of Smears

Service Treating Patient	Total Series			Pulmonary Series			Gastric Series		
	% from Source	% with Tumors	% of Tumors	% from Source	% with Tumors	% of Tumors	% from Source	% with Tumors	% of Tumors
Tuberculosis	43	5.3	15.8	59	5.3	21.5
Gastroenterology	20	3.2	4.5	74	16	100
Medical	23	30	52	27	29	55	13
Surgical	9	34	23	8	31	17.6	12
Others	5	4	4.5	6	15	5.9	1
Sex									
Male	65	17.2	82	70	18.8	90	54	11.6	53
Female	35	7.2	18	30	4.7	10	46	11.8	47
Age by Decades									
0-39.....	21	1	1.5	21	0	0	20.4	3.8	6.7
40-49.....	22	10.5	16.7	23	11.2	17.6	19.5	8	13.3
50-59.....	20.5	17.2	25.7	22	13	27.5	17.2	7.4	20
60-69.....	22.2	20.7	33.3	21	23	33.3	25	6.4	33.3
70-79.....	12.2	24.1	21.2	11	26	19.6	15.6	20	26.7
80 and over.....	2.1	10	1.5	2	2.6	2	2.3	0	0

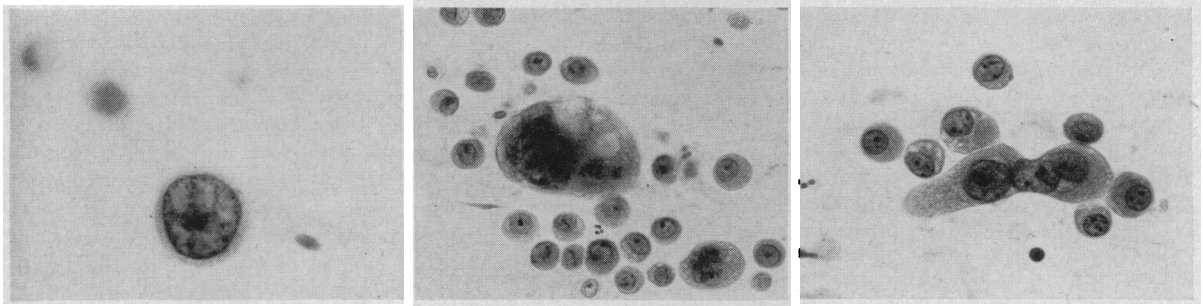


Figure 1. *Left*—A solitary huge malignant cell compared with the normal columnar epithelial cell. Note the nucleus-cell ratio (nuclear predominance), abnormal nuclear clearing ("moth-eaten") and large, abnormally shaped nucleolus. $\times 1100$. *Center*—Multinucleated giant-cell. Note size compared to leukocytes, nucleus-cell ratio, multiple, irregular, crowded nuclei, abnormally large nucleoli, and huge cytoplasmic vacuole. Also note individual malignant cells whose nuclei vary in size, shape and contour with variation of the chromatin granules in size, shape, density and distribution. $\times 500$. *Right*—A cell group. Note crowding, large nuclei varying in size and shape, with increased nucleus-cell ratio, prominent nucleoli, and clumping of chromatin. Also foamy cytoplasm. $\times 575$.

HISTOLOGY

Histologic classification was possible in 46 of the 49 proven cases. The 34 pulmonary lesions are classified below. In one of the two instances in which the type of lesion was completely undetermined, the presence of the growth was proven by pleural metastasis and by x-ray and clinical evidence, and in the other a widespread nonresectable tumor was observed at thoracotomy (the biopsy specimen was lost).

Primary:

Squamous cell carcinoma.....	25
Adenocarcinoma.....	2
Unclassified*.....	5

Secondary:

Adenocarcinoma of pancreatic origin.....	1
Signet ring carcinoma, source unknown.....	1

The gastric tumors were adenocarcinoma with the exception of one of the lesions in the "missed" cases, which proved to be a reticulum cell sarcoma. Interpretation of impression smears from the cut surface of the tumor itself was impossible. In one case diagnosis was on the basis of observation, at operation, of a large inoperable posterior gastric tumor with carcinomatosis peritonei, without microscopic biopsy.

CYTOLOGY

Some mention of the most frequently noted features of the tumor cells might be helpful. Single malignant cells rather than groups were commonest among the predominantly squamous, pulmonary cases. However, groups were observed in cases of suspected and proven adenocarcinomata of both pulmonary and gastric origin. Well defined pulmonary types such as Graham's¹⁵ differentiated "fiber" and "tadpole" cells were fairly common, but the most numerous were Graham's so-called "third type." These defy strict definition but they have multiple cytoplasmic and nuclear malignant qualities in varying combinations. Their order of importance among 20 cells photographed as typical examples follows:

1. Increased cell size and irregular shape..... 14
2. Increased size of nucleus in relation to size of cell (over 1:2 in cells larger than 10 microns)..... 12
3. Irregular nuclear contour..... 12
4. Hyperchromatism (especially with abnormally coarse, irregular, unequal chromatin granules, uniformly distributed)..... 12
5. Abnormally dense cytoplasm..... 6
6. Abnormal nucleoli..... 5
7. Vacuolated cytoplasm (not an independent criterion of malignancy, but of corroborative value)..... 3

The malignant features of exfoliated cell groups are more easily discerned. These were, in decreasing order of frequency, (1) variations in nuclear size, density, shape, and nucleoli; (2) clumping, distinguished by coherence of cells; (3) crowding with mutual deformity of adjacent cells; (4) cannibalism; and (5) malignant pearl formation.

The following examples were chosen for the cytological criteria of the malignant disease illustrated rather than for their clinical or critical value.

CASE REPORTS

CASE 1. A 61-year-old white male with many previous hospital admissions for arteriosclerotic heart disease and pneumonia entered the Los Angeles County Hospital January 4, 1950, with signs of cardiac failure and pneumonia which did not clear. A productive cough was prominent. Body weight declined 20 pounds in the ensuing four weeks. In bronchoscopic examination on February 3, 1950, a thin, sharp, mobile carina was noted. The right main bronchus was normal and there was purulent material in the left. The mucosa was edematous and freely bleeding throughout and the capillary vessels were distended. There was thickening of the spur dividing the left secondary bronchi but report on a biopsy specimen from this area was negative for cancer. A definite pleural exudate was noted on February 7, 1950, and the patient was scheduled for thoracentesis, but died February 14, 1950, before this could be done. Permission for autopsy was given too late. (For cytologic features, see Figure 1.)

CASE 2. A 57-year-old female entered Los Angeles County Hospital June 14, 1950, with complaints of bloating and epigastric fullness with constant pain for four months and ten-pound loss in weight in three months. In x-ray films a prepyloric defect was noted, and in gastroscopic examination a polypoid neoplasm was observed in the antrum on the greater curvature. In smears made at this time malignant

* In two of the five cases the report was "undetermined" from confirmatory biopsy—presumably anaplastic; and in the other three it was "highly anaplastic" at autopsy; "highly anaplastic" in lymph node biopsy, and "probable oat-cell carcinoma" on biopsy.

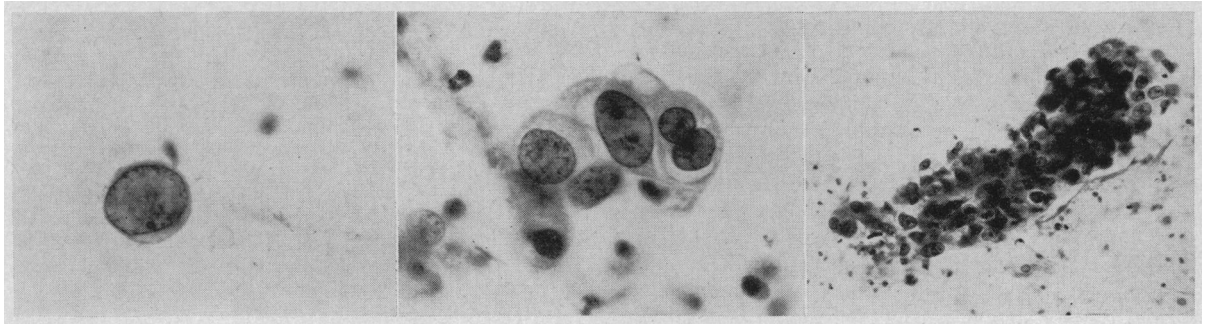


Figure 2. *Left*—A single huge cell compared with the small round cells. Note the nucleus-cell ratio, prominent nuclear membrane, and abnormally cleared areas associated with hyperchromatism, giving a moth-eaten appearance. $\times 1100$. *Center*—Clumped cells. Note coherence, vacuolization, and abnormalities in nuclear size, shape, density, and distribution of chromatin granules. $\times 1000$. *Right*—Large clump with evident coherence, crowding, vacuolization and many aberrations in nuclear details. $\times 440$.

cells and cell-groups were noted (Figure 2). Subtotal gastric resection failed to eradicate a grade IV adenocarcinoma with metastases to regional lymph nodes.

DISCUSSION

Of the many analyses of smear cytology, comparatively few dwell on the clinical usefulness of the method in terms of diagnosis of the presence of pulmonary tumors. Watson and co-workers¹⁶ studied 1,200 cases, in 236 of which there was bronchogenic carcinoma. Of the total 141 were detected by the smear technique, a "yield" of 8.5 per cent for the series. Farber and co-workers² reported positive diagnosis by examination of smears in 9.8 per cent of cases in a series of 2,066.

Liebow,⁶ in a review of pulmonary cases, considered the omission of the large proportion of cases in which there was no cancer improper for a truly critical analysis. Not to enter this controversy, the present report is presented to show that worthwhile "yields" may be anticipated by this method applied to selected groups of patients. Its obvious limitations as a mass screening test, in comparison to chest x-ray, for example, have led many physicians to reject it as altogether valueless.

The demonstrable increase in pulmonary carcinoma,¹² 0 to 2.3 per cent from 1918 to 1946, and the virtually assured 2 per cent incidence of gastric cancer in patients examined postmortem in the Los Angeles County Hospital, emphasize the value of a test which, even when incidentally employed, detects cancer of the lung in 80 per cent of cases in which such lesions are present, and gastric cancer in 60 per cent. The results reported herein, admittedly fortuitous, and also those of more experienced workers,¹³ indicate that with practice and conservatism, the one great hazard of false positive diagnoses may be practically eliminated.

Ferguson⁴ expressed the opinion that false-positives should be expressed as a percentage of the total positive reports, rather than of the total series. Thus, three false-positive and seven true diagnoses out of 100 cases would be 30 per cent instead of the customary 3 per cent. This would appear to be simply a matter of definition of terms in a survey of essentially normal individuals, but in a practice in which

many of the patients have non-cancerous disease characterized by atypical and metaplastic cells, such a classification seems unfair. The pathologist who must distinguish between the abnormal cells of bronchiectasis and those of malignant tumors is not faced with the simple dichotomy, is it cancer or is it normal? Rather, the problem is, is the abnormality malignant or is it benign? Lesions which may be biopsied only by expert endoscopists, if at all, may often be detected by examination of specimens which can be obtained without special equipment or skill and with a minimum of patient cooperation.

Graham and co-workers¹⁵ expressed belief that sputum has distinct advantages over bronchial secretion: "The laboratory can exercise more rigid control over the preparation of the smear. Repeated specimens of sputum can be obtained with greater ease. Finally, patients presenting definite enough symptoms to justify bronchoscopy have, too often, far advanced disease."

Watson and co-workers¹⁶ compared the 60 per cent accuracy of smears (112 sputum and 29 bronchial secretions "positive," out of 236) in bronchogenic carcinoma with 36 per cent "positive" biopsies on bronchoscopy (63 out of 176), and 86 per cent "positive" aspiration biopsies (85 out of 98). In 18 cases, seven of which proved operable, the preoperative "histological" proof depended upon cytology alone. In the series here reported upon, two cases were diagnosed by smear in the presence of "negative" biopsies, and the presence of malignant lesions was later proven by operation and autopsy. Herbut⁵ reported a series of 118 cases of pulmonary carcinoma in which 32 (27 per cent) were detected by smear but missed on bronchoscopy. In the present series the results with sputum alone (14 per cent yield) appear poorer than with a single bronchial specimen alone (21 per cent yield). However, the disproportionately great number of patients with tuberculosis in the series (59 per cent) distorts the relationship. Later experience has led to the conviction that a series of at least five specimens of sputum is superior to bronchial secretions. The 80 per cent over-all smear sensitivity which the authors claim for a series including some histologically unproven cases is less than the 89 per cent of Herbut,⁵

about equal to the 80 per cent of Farber² and somewhat higher than the 60 per cent of Watson and co-workers.¹⁶ Therefore, if 14.6 per cent of a selected group of patients harbor pulmonary tumors, of which 80 per cent are detectable by smears, prepared only incidentally in connection with another procedure and collected in part in an indifferent fashion, how much more valuable might this service become with increased ability on the part of the laboratory and increasing interest on the part of the clinician?

The difficulties in the cytological diagnosis of gastric cancer are suggested by Richardson's¹¹ observation that by using a cyto-histological preparation of gastric washings, he can distinguish acute, chronic and atrophic gastritis, ulceration and carcinoma. He reported an accuracy for carcinoma of 48.1 per cent with 3.9 per cent "false positive." Ulfelder and co-workers¹⁴ successfully diagnosed, by smear, 12 out of 14 cases of gastric cancer proven at operation. Pollard and co-workers¹⁰ reported that in a series of 278 cases in which there were 41 histologically proven neoplasms, they successfully diagnosed 35 per cent by smear, with 12 per cent indefinite. Bryant, Craig and Pollard¹ reported positive diagnosis in 41 per cent of 61 cases in which there was histological proof of cancer. In the present series the diagnosis of 60 per cent of the 11.7 per cent of malignant tumors in a selected group of patients is conditioned by the facts that in two cases anatomical proof was lacking, and one of the "missed" lesions was an undiagnosable reticulum cell sarcoma. It is apparent that much less accuracy and reliability is possible with gastric smears than with pulmonary. However, considering the simplicity of the test in comparison with gastroscopy and x-ray study, and the admitted unreliability of all three methods in establishing the malignant nature of a lesion, it seems reasonable to employ smear examination equally, as a source of corroborative information at least.

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